UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/752,231	12/29/2000	Abraham Grossman	Q01/006	4570

7590 11/05/2003

Anthony J. Janiuk, Esq.
Q-RNA, Inc.
Suite 407
3960 Broadway
New York, NY 10032

EXAMINER	
GOLDBERG, JEANINE ANNE	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 11/05/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/752,231	GROSSMAN, ABRAHAM	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *14-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *503* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to the papers filed June 24, 2003. Currently, claims 1-18 are pending. Claims 14-17 have been withdrawn as drawn to non-elected subject matter.

Election/Restrictions

2. Applicant's election of Group I, Claims 1-13 in the paper filed June 24, 2003 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 14-17 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement.

The requirement is still deemed proper and is therefore made FINAL.

This application contains claims 14-17 drawn to an invention nonelected with traverse. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Priority

3. This application claims priority to PCT/US99/15030, filed July 1, 1999 and provisional application 60/091,578, filed July 2, 1998.

Drawings

4. The drawings are objected to. Figure 1 contains a sequence which is not identified by SEQ ID NO: in either the brief description of the drawings or on the figure itself. Appropriate correction is required. The sequence appears as though it may be SEQ ID NO: 1.

Claim Objections

5. Claim 1 is objected to because the claim contains more than one period. For example, Claim 1 contains two steps. Each of the steps recites "a.)" and "b.)" Thus, Claim 1 contains more than one period and is objected to. The objection may be easily overcome by amending the claim to recite "a)" and "b)".

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 5, 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim 5 is indefinite with respect to the recitation "non-selective with respect to the template." Claim 5 depends from Claim 4 which specifically recites QB replicase, for example. It is noted that QB replicase is able to amplify and replicate RNA templates. Therefore, QB replicase is not exclusive to a single template. It is unclear whether Claim 5 further limits Claim 4 or whether the claim is intended to modify QB replicase to be non-selective in some way. Therefore, it is unclear whether the claim fails to further limit or whether the claim is intended to require an alteration of the RNA polymerase to ensure non-selectivity with respect to the template.

B) Claim 9 lacks proper antecedent basis because the term "the composition of the vessel" is unclear. It is unclear what "the composition of the vessel" is intended to refer to. It is unclear what composition is required. The claims set forth numerous compositions, and it is not clear which composition is required for the instant claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Brown et al. (Biochemistry, Vol. 34, pages 14775-14782, 1995) as evidenced by Brown-2 et al. (Biochemistry, Vol. 34, pages 14765-14774, 1995).

Brown et al (Biochemistry, Vol. 34, pages 14775-14782, 1995) teaches a method of selection and characterization of RNAs replicated by QB replicase. Brown teaches a method of making a replicatable RNA template having a selected affinity to a target comprising applying a selection to a first generation comprising a replicatable RNA template using a RNA polymerase to form replicatable RNA templates where the selection is based on the affinity of replicatable RNA template of different generations to said target. Brown also teaches a method of separating the replicatable RNA templates on the basis of the affinity of the replicatable RNA template to the target. Specifically, the method of Brown uses RNA populations, incubates the populations with QB replicase, a RNA polymerase to generate replication products, i.e. different generations of RNA (limitations of Claim 4, 10-11). The replication products were separated by electrophoresis and the correct-sized RNAs were purified (limitations of Claims 3, 6, 7). The purified replicatable RNA was used to initiate a subsequent round of replication, such that the overall level of dilution was sufficient to rid the population of RNA of all of the molecules that had been in the initial random population such that the final population of RNAs consisted entirely of sequences that had arising via replication of QB replicase (limitations of Claim 8-9). Therefore, the original RNA population separated RNA templates on the basis of affinity of the RNA template to QB replicase (page 14776, col. 1). Brown also teaches performing binding curves of QB replicase for

the various RNAs in the absence of nucleotides using filter binding assays with nitrocellulose filters (page 14776, col. 2). The binding reactions containing RNA, a reagent, and replicase, a RNA polymerase, were incubated and binding reactions containing replicase was vacuumed through nitrocellulose filters (limitations of Claim 2-3). The filters were dried and bound RNA was quantitated (pages 14776, col. 2). Inhibition and competition studies were also performed.

Claim 3 may be interpreted to mean that the fixed medium, an electrophoresis gel, is provided with a solution which comprises reagents and RNA polymerase prior to running the gel. The claim also would be interpreted to read that the "correct-sized RNA" products of the replication reaction were acrylamide gel band purified (page 14776, col. 1) and subjected to further reagents and RNA polymerase. Moreover, the claim could be broadly interpreted to read on a filter binding assay which subjected the QB replicase solution with a filter to determine the binding curves.

With respect to Claim 5, as discussed above, it is unclear what is meant by non-selective with respect to the template. It is noted that QB replicase is able to amplify and replicate RNA templates. Therefore, QB replicase is not exclusive to a single template.

Claim 9 has been broadly interpreted to mean that the replicase was applied to several vessels in subsequent rounds. The claim could also be interpreted to mean applying the selection to various lanes of the electrophoresis gel. The claim has thus been interpreted as broadly as reasonably possible.

With respect to Claim 12, as discussed above, it is unclear what is meant by the target is incorporated into one or more subunits of the polymerase. It is noted that QB replicates is an RNA which has enzyme activity. Q-beta replicase is a viral RNA polymerase secreted by a bacteriophage that infects *E. coli*. It has the property of being able to copy RNA sequences at a rapid rate. To the extent that the target is QB replicase, the target and the polymerase are incorporated.

With respect to Claim 13, Brown-2 teaches that the minus strand of QB can be replicated in vitro by a replicase preparation lacking not only the host factor but ribosomal protein S1 as well. This observation suggests that an RNA binding site for minus strand recognition exists on one of the three remaining subunits (page 14765, col. 2). The elements of the target QB replicase are covalently bound to each other, thus, the target is covalently bonded to the catalytic entity.

8. Claims 1-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Kawasaki (US Pat. 5,643,768, July 1997) as evidenced by Brown-2 et al. (Biochemistry, Vol. 34, pages 14765-14774, 1995).

Kawasaki teaches a method of cell-free synthesis and isolation of novel genes and polypeptides. Kawasaki teaches a method of making a replicatable RNA template having a selected affinity to a target comprising applying a selection to a first generation comprising a replicatable RNA template using a RNA polymerase to form replicatable RNA templates where the selection is based on the affinity of replicatable RNA template of different generations to said target. Kawasaki also teaches a method of separating the replicatable RNA templates on the basis of the affinity of the replicatable RNA

template to the target. Specifically, the method of Kawasaki teaches 1) generating an expression unit which contains an RNA polymerase binding sequence, a ribosome binding site, and a translation initiation signal, 2) generating semi-random DNA or RNA sequences and inserting the semi-random sequences into the expression unit 3) transcribing novel genes in vitro to produce a pool of RNA copies which may be produced by a replicase is an RNA polymerase sequence is included 4) translating the RNA in vitro to produce polysomes which keep the polypeptide and mRNA together 5) allowing the polysomes to bind to substances of interest such as receptor proteins, toxins, antibodies, hormones etc. 6) enriching polysomes which bid to the substance of interest using serial or flow-through washes 7) disrupting the bound/active polysomes to release the mRNAs from the polysome complex 8) recovering and amplifying the RNA with RNA directed RNA polymerases (col. 3-4)(limitations of Claim 1). Kawasaki indicates that repetition of replication and binding proteins is preferred to increase the frequency of specific binding proteins above a background of nonspecific binding of polysomes. Kawasaki also teaches that an advantage of the RNA expression unit is that the recovery of the polysomal mRNA does not have to go through cDNA state. MRNA with the desired sequences may be amplified with RNA directed RNA polymerase such as QB replicase (col. 7, lines 20-30)(limitations of Claim 4). When the QB replicase template is transcribed, an RNA library capable of in vitro replication may be created with contains the semi-random gene sequences (col. 7, lines 35-40). Kawasaki teaches using a fixed medium in which target substances of interest are "stuck" the membranes. Before the polysomes are allowed to bind to the substances of

interest, a screen may be performed which bind generally to the target to enhance the specific binding. After the polysomes are selectively bound to the substance of interest, nonbonding polysomes are removed by washing (col. 13, lines 15-20)(limitations of Claim 2, 6-7). As specifically illustrated in the Examples, polysome binding to antibodies is performed with immobilization of antibodies. The antibodies may be used to select novel binding peptides (col. 21, lines 42-48). The antibodies are affixed to a membrane (col. 21, lines 65-68). The polysomes with nascent semi-random peptides are incubated with the mixture (col. 22, Example 5)(limitations of Claim 3). The membrane which holds the washed antibody-bound polysomes is transferred to a tube (i.e. second fraction having said target containing replicatable RNA templates having higher affinity than RNA templates in the first fraction)(limitations of Claim 6, 7). As provided above, repetition of the steps 3-9 is preferable to further increase the frequency of specific binding proteins (col. 4, lines 35-40)(limitations of Claim 8-9).

With respect to Claim 5, as discussed above, it is unclear what is meant by non-selective with respect to the template. It is noted that QB replicase is able to amplify and replicate RNA templates. Therefore, QB replicase is not exclusive to a single template.

Claim 9 has been broadly interpreted to mean that the replicase was applied to several vessels in subsequent rounds. The claim has thus been interpreted as broadly as reasonably possible.

With respect to Claim 12, as discussed above, it is unclear what is meant by the target is incorporated into one or more subunits of the polymerase. It is noted that QB

replicates is an RNA which has enzyme activity. Q-beta replicase is a viral RNA polymerase secreted by a bacteriophage that infects *E. coli*. It has the property of being able to copy RNA sequences at a rapid rate. To the extent that the target is QB replicase, the target and the polymerase are incorporated.

With respect to Claim 13, Brown-2 teaches that the minus strand of QB can be replicated in vitro by a replicase preparation lacking not only the host factor but ribosomal protein S1 as well. This observation suggests that an RNA binding site for minus strand recognition exists on one of the three remaining subunits (page 14765, col. 2). The elements of the target QB replicase are covalently bound to each other, thus, the target is covalently bonded to the catalytic entity.

Conclusion

9. No claims allowable over the art.

10. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

A) Burke et al. Teaches in vitro selection and evolution of RNA using initial population s of RNA variants. Burke teaches that RNA molecules with binding activities are separated from those that do not bind by using immobilized ligands in a procedure analogous to affinity chromatography.

B) Coia et al (US Pat. 6,562,622, May 13, 2003) teaches continuous in vitro evolution. The claimed method of Coia is directed to incubating a replicable mRNA molecules with an RNA-directed RNA polymerase to introduce mutations, incubating the

mutant mRNA molecules with a translation system to form mutant/mRNA complexes, selecting one or more mutant protein/mRNA complexes by exposing the population to the target molecule and recovering the mutant protein/mRNA complexes bound thereto.

Coia is not prior art.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

J. Goldberg

Jeanine Goldberg
Patent Examiner
November 3, 2003